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REMARKS

The Office Action

Claims 1-6, 9, 10, and 21-25 are under examination in this case. Claims 1-6, 9, 10, and 21-24 stand rejected under 35 U.S.C. § 103. This rejection is addressed below.

Claim Amendments

Claim 25 has been amended. It is now presented as an independent claim that no longer refers to claim 1. No new matter has been added by this amendment.

Rejections under 35 U.S.C. § 103(a)

Claims 1-6, 9, 10, and 21-24 stand rejected under 35 U.S.C. § 103 as being unpatentable over Kovesdi (US 2003/0045498) in view of Morsy (PNAS 95: 7866-7871, 1998) or further in view of Tezel (Exp. Eye Res. 66: 807-815, 1998). These rejections are respectfully traversed.

The current claims are directed to a pigment epithelial cell of the eye that includes adenoviral vector DNA having at least one expressed nucleic acid operatively linked to a promoter. The vector includes neither adenoviral nor *E. coli* coding DNA sequences. Applicants' vector represents a significant advance in the area of adenoviral vector technology because removal of the adenoviral coding sequences allows the vector to carry very large segments of foreign DNA, while surprisingly the vector is still capable of transducing pigment epithelial cells of the eye. In addition, the absence of *E. coli* vector sequences, which are generally immunogenic in mammalian hosts, allows for the optimized use of Applicants' claimed vector in therapeutic applications. Neither this vector, its use for transducing pigment epithelial cells of the eye, nor the particular methods for cultivating those transduced cells are suggested by the prior art.

The current rejection reverts back to relying primarily on a reference by Kovesdi, a reference previously addressed by Applicants and reliance on which was earlier dropped

by the Office. Kovesdi generally describes a variety of vectors expressing a particular protein, PEDF, for the treatment of ocular-related disorders. Among the vectors mentioned by Kovesdi is an adenoviral vector that is deficient for the E1, E2, E3, and E4 viral coding sequences, but possessing the L region of the adenoviral genome. Moreover, in Kovesdi's working examples, vectors deleted for E1 and E3 or E1, E3, and E4 are utilized. These vectors include both the E2 and L coding regions. Kovesdi therefore provides no information on whether adenoviral vectors lacking *all* adenoviral sequences, as required by the claims, would be capable of transduction and transgene expression in pigment epithelial cells of the eye.

The secondary reference, Morsy, also fails to provide this aspect of the claims. Morsy discloses HD vectors (gutless adenoviral vectors) and their use for expressing the leptin gene, a gene involved in blood insulin and glucose levels and weight regulation. In Morsy, the vector is administered systemically into the tail vein of animals, and expression is measured in blood plasma. Morsy's experiments relate in no way to pigment epithelial cells of the eye, and Morsy therefore provides no information on whether their HD vector would or could transduce such cells or support transgene expression. Contrary to the Office's basis for this rejection, therefore, the cited references do not support a *prima facie* case of obviousness because, even in combination, the references fail to provide a reasonable expectation of success for use of HD vectors in pigment epithelial cells of the eye. For this reason, the § 103 rejection should be withdrawn.

Moreover, nothing in Kovesdi or Morsy forecasts the surprising results obtained by Applicants. The present inventors unexpectedly obtained persistent gene expression for *four months* in animal models after transplantation of retinal pigment epithelial cells including Applicants' high capacity adenoviral vector DNA, and for *six months* after direct transduction with such adenoviral vector *in vivo*. This long term expression after gene transfer into pigment epithelium of the eye by use of the claimed vectors including

neither adenoviral nor *E. coli* coding DNA sequences could not have been anticipated and would clearly be considered a surprising and therefore unexpected result to a person skilled in the art.

The Office points out that Morsy teaches that "the greater safety, efficient gene delivery and increased insert capacity of HD vectors (gutless adenoviral vectors) are considerable improvements over current adenoviral vectors and represent favorable features especially for clinical gene therapy applications." Notably, these advantages listed by Morsy do not include long term expression, consistent with Applicants' position that the long term expression feature possessed by the claimed vectors was not anticipated by those in the art. In addition, in Morsy et al., leptin gene expression obtained from their HD-leptin vector was no longer detectable after only 8 weeks (see Morsy, page 7870, right column, last complete sentence and Fig. 5D). This experimental result as well highlights the surprising feature of the claimed vectors: that Applicants' vectors transduce and support long term transgene expression. As indicated, Applicants' claimed vectors support an expression profile in pigment epithelial cells of the eye that exceeds the time period achieved in Morsy in serum by 200%. In view of this clear surprising and unexpected result, the § 103 rejection of claims 1-6, 9-10 and 21-24 should be withdrawn. Reconsideration on this issue is requested.

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Conclusion

Applicants submit that all claims are now in condition for allowance, and such action is requested.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 19 December 2006

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